REMARKS

The June 2, 2010 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, a shortened statutory response period of three (3) months was set forth in the June 2, 2010 Official Action. Therefore, the initial due date for response was September 2, 2010. A petition for a two (2) month extension of the response period is presented with this response, which is being filed within the two month extension period.

The Examiner has rejected claims 38, 39, 41-47, 54, and 55 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S Patent Application Publication No. 2001/0001040 in view of U.S Patent 5,902,610.

Claims 53 and 56 have also been objected to as being dependent on a rejected base claim. The Examiner states that claims 53 and 56 would be allowable based on the elected species of 1-MT, methyl-TH-DL-Trp, and cisplatin, if rewritten in independent form to include all of the features of the base claim and any intervening claims.

The foregoing objection and rejection constitute all of the grounds set forth in the June 2, 2010 Official Action for refusing the present application.

In accordance with the instant amendment, withdrawn claims 1-37, 40, and 48-52 have been cancelled without prejudice to Applicants' right to file one or more continuing applications, as provided in 35 U.S.C. §120, on the cancelled subject matter. Applicants have also amended claims 38, 47, and 55. Support for the amendment to claim 38 can be found throughout the application including, for example, previous claim 53. Support for the amendment to claims 47 and 55 can be found throughout the application including, for example, claim 47. In accordance with the instant amendment, claims 57-66, which read on the elected species, have been added. Support for new claims 57-66 can be found throughout the

application including, for example, claims 38, 39, 41-47, and 53-56. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 38, 39, 41-47, 54, and 55 and the objection of claims 53 and 56, as set forth in the June 2, 2010 Official Action, cannot be maintained. These grounds of objection and rejection are, therefore, respectfully traversed.

THE CLAIMS ARE NOT RENDERED OBVIOUS BY THE '040 APPLICATION IN VIEW OF THE '610 PATENT

The Examiner has rejected claims 38, 39, 41-47, 54 and 55 under 35 U.S.C. §103(a) as allegedly unpatentable over the '040 application in view of the '610 patent. The '040 application allegedly discloses that IDO inhibitors including 1-MT are useful in the treatment of cancer. The '610 patent allegedly teaches that cisplatin is an anticancer agent that is effectively used against a broad spectrum of cancers. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the above disclosures to arrive at the instantly claimed invention.

At the outset, independent claim 38 from which claims 39, 40, 43-47, 55, and 56 depend, has been amended to recite that the IDO inhibitor is methyl-TH-DL-Trp. The references cited by the Examiner fail to teach or suggest the use of methyl-TH-DL-Trp for the treatment of cancer. Indeed, claim 53, which previously recited that the IDO inhibitor is methyl-TH-DL-Trp, was not included in the instant rejection and was only objected to for depending on a rejected base claim.

New claims 57-66 recite that the IDO inhibitor is 1-methyl-DL-tryptophan. At page 4 of the instant Official Action, the Examiner acknowledges that "Applicant has provided evidence of an unexpected synergistic anti-cancer activity of

the instantly claimed method" wherein the IDO inhibitor is 1MT, the chemotherapeutic agent is cisplatin, and the cancer being treated is breast cancer. Applicants note that new claim 66 recites that the IDO inhibitor is 1MT, the chemotherapeutic agent is cisplatin and the cancer is breast cancer. The Examiner, at page 4 of the instant Official Action, states that "objective evidence of non-obviousness must be commensurate in scope with the claims" and asserts that Applicants have failed to provide evidence of "unexpected synergistic anti-cancer activity" with other species. Applicants respectfully disagree for the reasons of record and those set forth below.

New claim 65 recites methods of treating breast cancer by administering the IDO inhibitor 1MT and at least one chemotherapeutic agent. As stated hereinabove, the Examiner has acknowledged that when the chemotherapeutic agent is cisplatin, Applicants have demonstrated unexpected synergy. However, Applicants have also clearly demonstrated unexpected synergy with other chemotherapeutic agents.

As stated in the July 7, 2008 and July 2, 2009 Official Action responses, Figure 11 of the instant application demonstrates that the administration of 1MT or paclitaxel alone only mildly slowed the growth of the breast cancer. In stark contrast, the co-administration of 1MT with paclitaxel caused the tumor to shrink significantly. This is an unexpectedly superior result with significant benefits and positive implications for the treatment of cancer. Applicants also previously submitted Kumar et al. (J. Med. Chem. (2008) 51:1706-1718) and Muller et al. (Nature Medicine (2005) 11:312-319)', which provide further evidence of the unexpected synergy with the co-administration of 1MT and paclitaxel against breast cancer.

Applicants also previously submitted Hou et al. (Cancer Res. (2007) 67:792-801) as providing evidence that the co-administration of 1MT with chemotherapeutic agents led to unexpectedly synergistic treatment of breast cancer. As

stated in the July 7, 2008 Official Action response, Figure 2A of Hou et al. demonstrates that 1MT alone did not significantly reduce breast tumor size and cyclophosphamide administered alone only mildly reduced the breast tumor size. In contrast, co-administration of 1MT and cyclophosphamide demonstrated unexpected synergy and reduced the breast tumor to an undetectable size. Similar results were obtained with another breast cancer and the co-administration of 1MT and paclitaxel (Figure 2B).

As explained in the January 15, 2009 Official Action, Figure 5 of the instant application demonstrates that breast tumors increased in volume after a two week course of 1MT. Similarly, breast tumor volume was also shown to increase when doxorubicin (particularly at 0.66 mg/day) was administered alone over a two week course. In complete contrast, Figure 5 of the instant application shows the unexpectedly superior finding that the co-administration of 1MT and doxorubicin led to a *reduction* in breast tumor volume over a two week course.

In view of the foregoing, Applicants have clearly demonstrated unexpectedly superior synergy through the co-administration of the IDO inhibitor 1MT with four different chemotherapeutic agents (cisplatin, paclitaxel, cyclophosphamide, and doxorubicin). It is also noteworthy that these chemotherapeutic agents work via different mechanisms. Indeed, cisplatin is a platinum based DNA cross-linker, paclitaxel is a mitotic inhibitor as it stabilizes microtubules, cyclophosphamide is a nitrogen mustard alkylating agent which leads to DNA crosslinking, and doxorubicin is an anthracycline antibiotic which intercalates DNA. Based on the finding that unexpected synergy was observed with 1MT and these chemotherapeutic agents having very different mechanisms of action, a skilled artisan would ascertain a trend that would allow him/her to reasonably believe the unexpectedly superior properties would exist for the genus of chemotherapeutic agents. Applicants respectfully remind the Examiner that the MPEP at §2145 states:

> When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness. Id.
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> For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.)

In view of all of the foregoing, it is without question that the co-administration of 1MT with a chemotherapeutic agent produces unexpectedly superior results in terms of inhibiting breast tumor growth and, therefore, the treatment of breast cancer.

Having demonstrated the unexpectedly superior results from the co-administration of 1MT with a chemotherapeutic agent in breast cancer, Applicants also demonstrated that these results were observed in numerous other cancers.

As explained in the July 7, 2008 Official Action response, the data provided in Hou et al. also demonstrates the unexpectedly superior results obtained from the co-administration of 1MT with a chemotherapeutic agent in melanoma. Indeed, the melanoma tumor volume observed in mice treated with either 1MT or the chemotherapeutic agent cyclophosphamide alone is the same after 28 days as mice who received no treatment at all. In stark contrast, the co-administration of 1MT with cyclophosphamide reduced the melanoma tumor volume by almost 70% compared to untreated

animals (Figure 1A).

Applicants also submitted a Declaration by co-inventor Dr. George Prendergast with the July 7, 2008 Official Action response which demonstrated the unexpected synergy of 1MT with a chemotherapeutic agent in the treatment of other cancers. As previously explained (see, e.g., the July 7, 2008 and July 2, 2009 Official Action responses), the evidence provided with the Prendergast Declaration demonstrates that while the administration of 1MT or cyclophosphamide alone had little to no effect on the growth of lung or colon tumors, the co-administration of 1MT and cyclophosphamide greatly inhibited lung and colon tumor growth. Indeed, the data presented in with the Prendergast Declaration shows that the co-administration of 1MT and cyclophosphamide yielded greater tumor growth inhibition than the growth inhibition of the individual agents added together (the additive effect). Accordingly, the data provided with the Prendergast Declaration clearly demonstrates unexpected synergy with 1MT and a chemotherapeutic agent in colon and lung cancer.

As explained in the July 2, 2009 Official Action response, Hou et al. demonstrate that administration of 1MT with a chemotherapeutic agent resulted in an unexpected synergistic effect against melanoma. Figure 5A of Hou et al. shows that the co-administration of 1MT with cyclophosphamide inhibited melanoma tumor growth significantly more than the additive effect of the agents alone. Further, Figure 5B of Hou et al. also demonstrates that the synergistic effect is observed when the chemotherapeutic agent is gemcitabine (a nucleoside analog and, therefore, yet another different mechanism of action for a chemotherapeutic agent). Indeed, neither 1MT nor gemcitabine significantly changed the melanoma tumor area. In stark contrast, the co-administration of both agents resulted in significant tumor inhibition, thereby demonstrating unexpected synergy above the additive effect of the individual agents. Applicants also note that Figure 1C of Hou et al. demonstrates a synergistic effect when the

chemotherapeutic agent was replaced with irradiation.

Applicants also submit herewith El Kholy et al. (Med. Oncol. (2010) Epub ahead of print on March 19, 2010). El Kholy et al. state that the use of "1MT alone showed no significant inhibitory effect" on leukemia blast cells (see Abstract). While the use of doxorubicin (adriamycin) inhibited leukemia blast cell proliferation, more inhibition was observed when 1MT was co-administered with doxorubicin (see, e.g., Abstract). Indeed, El Kholy et al. state that their results demonstrate that "1MT potentiates the effects of [doxorubicin]," whereas there "was no significant inhibition of the proliferation of blast cells using 1MT alone" (page 8). El Kholy et al. also discuss the results provided by Muller et al. (Nature Medicine (2005) 11:312-319) and note the "synergy between IDO inhibitors and chemotherapy" (page 8). Indeed, El Kholy et al. generally recommend the use of IDO inhibitors such as 1MT with cancer vaccines and chemotherapy (page 8).

Applicants also submit herewith Inaba et al. (Gynecol. Oncol. (2009) 115:185-192). Figure 5C of Inada et al. demonstrates that in a murine ovarian cancer model, the administration of 1MT alone did not significantly increase mouse survival. "In contrast, the survival time was significantly ($p = 0.037$) prolonged in the mice that had been treated with 1-MT combined with weekly i.p paclitaxel at 20 mg/kg four times when compared to that of treatment with paclitaxel alone using the same schedule" (page 190). Inaba et al. conclude that "treatment with paclitaxel plus 1-MT synergistically prolonged mouse survival" in an ovarian cancer model. Accordingly, Inaba et al. demonstrate that the administration of 1-MT with a chemotherapeutic agent provides unexpectedly superior results in an ovarian cancer model.

In view of the foregoing, Applicants have provided evidence that 1MT combined with a chemotherapeutic agent provides unexpected synergy in at least six different cancers, namely: ovarian cancer, leukemia, melanoma, breast cancer, colorectal cancer, and lung cancer. Based on the finding that

unexpected synergy was observed in all of these different cancers (including blood cancers and organ/tissue cancers), a skilled artisan would ascertain a trend that would allow him/her to reasonably believe the unexpectedly superior properties would exist for the genus of cancer.

In view of all of the foregoing, Applicants respectfully submit that the rejection of claims 38, 39, 41-47, and 53-56 under 35 U.S.C. §103(a) is untenable and request its withdrawal.

CONCLUSION

In view of the foregoing remarks, it is respectfully urged that the objection and rejection set forth in the June 2, 2010 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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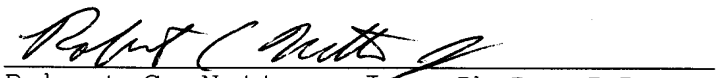
By 
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Enclosures: El Kholy et al., Med. Oncol. (2010) Epub ahead of print on March 19, 2010
Inaba et al., Gynecol. Oncol. (2009) 115:185-192